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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/009,823

Applicant(s)

PANACCIO ET AL.

Examiner

Padmavathi v. Baskar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-8, 10-11, 13-14 and 17-20, 21 and 39-45 is/are pending in the application.
- 4a) Of the above claim(s) 21, 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-8, 10-11, 13-14, 17-20 and 40-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION
Response

1. Applicant's response filed on 5/19/05 is acknowledged.

Status of claims

2. Claims 1, 6, 19 and 21 have been amended.

New claims 40-45 have been added.

Claims 5, 9, 12, 15-16 and 22-38 are canceled.

Claims 1-4, 6-8, 10 -11, 13-14 and 17-20, 21 and 39 —45 are pending in the application.

Claims 1-4, 6-8, 10 -11, 13-14, 17-20 and newly added claims 40-45 (claims read on the elected invention) are under examination

Claims 21 and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Claim objection withdrawn

3. In view of amendment to the claim 19, the objection of record is withdrawn.

Claim Rejection - 35 U.S. C. 112, first paragraph withdrawn

4. In view of clarification and arguments of record, the rejection of claims 13,14 and 19 under 35 U.S.C. 112, first paragraph (deposit) is withdrawn.

Priority date

5. This application is a 371 PCT/AU00/00043 filed on 5/11/2001, which claims priority to the U.S. Provisional application 60/133973, filed May 13, 1999.

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Claim Rejection - 35 U.S. C. 112, first paragraph maintained

6. The written description rejection of claims 1-4, 6-8, 10 -11, 17-18 and newly added claims 40-45 under 35 U.S.C. 112, first paragraph is maintained as set forth in the previous office action.

The specification describes as part of the invention, an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The specification teaches that the full-length protein comprises 502 amino acids as set forth in SEQ.ID.NO: 1 and is useful in diagnosing infection caused by *Lawsonia intracellularis* in pigs. However, the immunological function of this polypeptide in assessing *Lawsonia* infection has not yet been identified. Further, the specification does not disclose

1) an isolated or recombinant immunogenic polypeptide comprising a *Lawsonia spp* FlgE polypeptide, a variant, wherein said variant mimics or cross reacts with a B-cell or T-cell epitope of *Lawsonia spp* FlgE polypeptide and wherein said variant has at least about 60% overall sequence identity to the 502 amino acid sequence set forth in SEQ ID NO: 1.,

2) a vaccine composition comprising a *Lawsonia spp* FlgE polypeptide, a variant, wherein said variant mimics or cross reacts with a B-cell or T-cell epitope of *Lawsonia spp* FlgE polypeptide or

3) an isolated or recombinant immunogenic polypeptide or a vaccine composition comprising

i. a peptide, oligopeptide or polypeptide comprising 60% sequence identity to SEQ.ID.NO: 1

ii) a homologue (i) which mimics or cross-reacts with a B-cell or T- cell epitope of *Lawsonia spp* FlgE polypeptide or immunogenic homologue or derivative (the examiner considers all these variants and hereafter will be referred to variants). Therefore, said variants do not meet the guidelines on written description. The specification fails to disclose any substitution, insertion or deletion or change in (i) a polypeptide SEQ.ID.NO: 1 to obtain a variant having 60% identity to SEQ.ID.NO: 1 or variants or homologues of SEQ.ID.NO: 1. The specification does not describe any use of said variants as claimed (comprising, open language) in identifying *L.intracellularis* infection. None of the above variants meet the written description provision of 35 U.S.C. 112, first paragraph. *Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111*, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116).

Thus, the specification fails to teach the claimed variants and does not satisfy the written description guidelines because an isolated polypeptide comprising (open language) said variants plus unlimited and unknown amino acids of SEQ.ID.NO: 1 and an isolated polypeptide comprising an amino acid sequence having 60% sequence identity to SEQ.ID.NO: 1 plus unlimited and unknown amino acids would result in unknown variants without sufficient structure and completely lacking identifying characteristics such as function. Thus, variants as claimed are broader than SEQ.ID.NO: 1 and do not appear to have sufficient structural characterization and lack any identifying characteristics (function). Further, inducing an immune response is not an identifying characteristic

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(function) of a fragment because there are many fragments with the same function in a polypeptide and such variants are not distinguishable from each other. Thus variants as claimed are uncharacterized by this specification and are not asserted to belong to any known family of proteins such as outer membrane proteins of *L.intracellularis*. The specification fails to teach the structure or relevant identifying characteristics sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc V Chugai Pharmaceutical Co Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

The actual biological function of isolated FlgE polypeptide SEQ ID NO: 1 is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. USPQ2d 1111 makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See Vas-Cath at page 1116).

The specification only discloses FlgE polypeptide comprising the amino acid sequence SEQ ID NO: 1 which corresponds to the polynucleic acid sequence SEQ ID NO: 2. Thus, FlgE polypeptide comprising the amino acid sequence SEQ ID NO: 1 meet the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below. The specification fails to teach the claimed variants and they do not exist as an invention independent of their function in encoding a protein. The actual structure or other relevant identifying characteristics of each variant including homolog, analogue or derivative having the claimed properties can only be determined empirically by actually making every recited variability (i.e. variants,) and testing each to determine whether such a variant has any particularly disclosed properties of a protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function. This specification does not teach such variants, and the art is devoid of such said variants of SEQ ID NO: 1, with undetermined function. There is no written description support for variants as claimed.

Applicant's arguments filed on 5/19/05 have been fully considered but they are not deemed to be persuasive.

Applicant states the Examiner has rejected claims for the language referring to as "variants", "truncated variants" "peptide having at least about 60% sequence identity to SEQ ID NO: 1, immunogenic homologues or derivative" and applicant amended the claims to delete 'truncated variant' from the claims and the Specification provides

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considerable teaching of types of variants and ways of producing the variants as claimed because

(a) Figure 1 provides an amino acid alignment of various FlgE polypeptides with highly conserved as well as low conserved regions known in the art. (see Brief Description of the Drawings, Figure 1). This, in combination with the specification on page 8, paragraph 98 and page 5 paragraphs 71 and 72 which explains which areas in Figure 1 are useful,

(b) the definitions of Derivatives and analogues have been shown in page 16, paragraph 194 and page 7, paragraph 89, the substitution variants in page 7 paragraphs 80-88, the types of changes that can affect the epitope in page 6, paragraph 73, and amino acid substitutions page 4, paragraph 51. The skilled artisan has been given sufficient information about what types of variants would still cross react with a B-cell or T-cell epitope of *Lawsonia* spp. FlgE Polypeptide." Once produced or identified, the variants can be tested for cross-reactivity using the methods on page 3, paragraphs 42-44.

(c) the specification provides methods of using the polypeptides as vaccines for the treatment and prophylaxis of *L. intracellularis* infection. Because the field of vaccination and immunization is one of the earliest aspects of molecular biology to be identified, it has had a lengthy amount of time to gain a certain sophistication, while fields like immunology have lagged. Thus, the skilled artisan can be considered quite knowledgeable.

The examiner disagrees with the applicant because

(a) The newly amended claims reciting " --- said variant has at least about 60% overall sequence identity to the 502 amino acid sequence set forth in SEO ID NO: 1 or vaccine composition comprising ---60% sequence identity--, immunogenic homologues,

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or derivatives or variants of SEQ ID NO: 1 have not been disclosed in this specification. Figure 1 is a deduced amino acid sequence comparison of various bacterial FlgE polypeptides, wherein gaps have been introduced to optimize the alignment. The examiner understands that the specification discloses the SEQ.ID.NO: 1 and therefore, applicants are in possession of an isolated polypeptide comprising the amino acid sequence SEQ.ID.NO: 1. However, the specification does not disclose an "isolated polypeptide **comprising** (open claim language) **60% sequence identity to SEQ.ID.NO: 1, homologues or derivatives, ---**". These polypeptides as claimed are broader than SEQ.ID.NO: 1 and thus are not limited to any variant with a specific function. (b) While the specification teaches general method of substitutions, additions, deletions, the specification fails to teach the claimed fragments and do not satisfy the written description guidelines because an isolated polypeptide comprising (open language) **60% sequence identity** plus unlimited and unknown amino acids would result in an unknown polypeptide without any structure and other identifying characteristics such as specific function. Further, inducing an immune response and antibody cross react with B-cell or T-cell epitope is not an identifying characteristic (function) of a variant/derivative / homologue because there are many variants with the same function in a polypeptide and such variants are not distinguishable from each other. Thus variant/derivative / homologue as claimed (with open claim language) are uncharacterized by this specification. Further, isolated or recombinant a polypeptide or peptide or oligopeptide **comprising an** amino acid sequence of SEQ.ID.NO: 1 (for example claim 44) is not disclosed by structure, figure or diagram as per the Written Description Guidelines.

The specification on pages 6, 7, 8 and 16 discloses the amino sequence obtained from *L. intracellularis* are less highly conserved among homologous genes and polypeptides

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obtained from other species and is a preferred immunogen for diagnostic and vaccination protocols. However, no immunogenic variant from SEQ.ID.NO: 1 has been shown to be useful for vaccination or even diagnostic purposes. General methods of obtaining T-cell or B-cell epitopes have been discussed. However, no variant polypeptide or antibody from FlgE has been shown to be cross react with B-cell or T-cell epitope.

(c) While the general knowledge and skill in the molecular biology and immunology have been considerably improved, the protein chemistry and mechanism of protective immune response to bacterial pathogens are not disclosed in the art or by this specification, especially polypeptide, (SEQ.ID.NO: 1) *Lawsonia intracellularis*, a recently identified bacterial pathogen which causes disease in a broad range of animals including Pigs, Horses, Avian species, Macaques and Human population. It is apparent that this bacterium is an unique enteric pathogen and no host or bacterial factors, which contribute to proliferative enteropathy, have not yet been identified by this specification. Therefore, for the reasons of record this rejection is maintained.

7. The rejection of newly amended claims 1-4, 6-8, 10, 11, 13-14, 17- 20 and newly added claims 40-45 under 35 U.S.C. 112, first paragraph is maintained as set forth in the previous office action.

The specification, while enabling for an isolated polypeptide or a recombinant immunogenic polypeptide comprising the amino acid sequence SEQ ID NO: 1 or the amino acid sequence encoded by the FlgE-encoding nucleotide sequence of pALK11 (ATCC 207156) of *L.intracellularis* FlgE polypeptide or an immunogenic composition comprising the amino acids sequence SEQ ID NO: 1 the amino acid sequence encoded by the FlgE-encoding nucleotide sequence of pALK11 (ATCC 207156) of *L.intracellularis* FlgE polypeptide and one or more carriers, diluents or adjuvants suitable for veterinary or pharmaceutical use does not reasonably provide enablement for

1) an isolated or recombinant immunogenic polypeptide comprising a *Lawsonia* spp FlgE polypeptide, a variant, wherein said variant mimics or cross reacts with a B-cell or T-cell epitope of *Lawsonia* spp FlgE polypeptide,

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2) a vaccine composition comprising a *Lawsonia spp* FlgE polypeptide, a variant, wherein said variant mimics or cross reacts with a B-cell or T-cell epitope of *Lawsonia spp* FlgE polypeptide and

3) an isolated or recombinant immunogenic polypeptide or a vaccine composition comprising

i. a polypeptide comprising 60% sequence identity to SEQ.ID.NO: 1

ii) a homologue which mimics or cross-reacts with a B-cell or T- cell epitope of *Lawsonia spp* FlgE polypeptide

(the examiner considers all these variants and hereafter will be referred to variants).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for the full scope of claimed polypeptide SEQ.ID.NO: 1 variants because it fails to provide any guidance regarding how to make and use the variants (any amino acid sequence selected from an amino acid sequence which has 60% sequence identity to SEQ.ID.NO: 1 etc).

The instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention is preparing recombinant polypeptide from *L. intracellularis* only. The invention is drawn to an isolated protein as set forth in SEQ ID NO: 1 which is encoded by *L. intracellularis* polynucleotide, SEQ.ID.NO: 2 (pALK12, ATCC 207195). The specification also teaches that this full-length protein contains 502 amino acids. The specification discloses the claimed polypeptide could be used to identify *L. intracellularis* infection and as an immunogen and formulating the compositions in Freund's adjuvant to immunize mice for preparing antibodies.

The state of the art in *L. intracellularis* is devoid of making or using fragments of recombinant peptides or variants as claimed. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid sequences (i.e. fragments) for different aspects of biological activity cannot be predicted a priori and must be determined empirically on a case-by-case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and

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immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produces proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Thus, it is apparent that change in a peptide can lead to loss of binding property of that peptide.

The specification provides no working examples demonstrating (i.e., guidance) enablement for an isolated polypeptide comprising a sequence having 60% sequence identity to SEQ.ID.NO: 1, immunogenic composition comprising said variants of SEQ ID NO: 1. Furthermore, it is unclear whether isolated polypeptide comprising a sequence having 60% sequence identity to SEQ.ID.NO: 1 can be used for identifying *L. intracellularis* infection. Thus, peptides comprising *L. intracellularis* must be considered highly unpredictable, requiring a specific demonstration of efficacy on a case-by-case basis.

With respect to vaccine composition as recited in claims 17-20, the specification provides no information on the protective immunogenicity of the claimed polypeptide, fragments, the variants or the ability to protect the animal from disease. The specification fails to teach that the claimed polypeptide or fragments or variants are capable of generating a humoral or cellular immune response. The specification also fails to teach that the immune/antibody response to the polypeptide produced by the claimed polypeptide alone or in combination with adjuvants or carriers provides protection against infection in any acceptable animal model. Vaccines by definition trigger a protective immune response in the host vaccinated and mere antigenic response is insufficient to provide for enablement of vaccines. This specification fails to teach protective immune response generated by said isolated polypeptide --vaccine. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed polynucleotide encoding polypeptides or fragments thereof alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. The specification fails to teach that the claimed polynucleotide encoding a polypeptide peptide or fragment or variant thereof are able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize other similar nucleic acids as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. (*Genentech Inc. v. Novo Nordisk A/S Ltd.*, 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made-and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

The state of the art indicates that very little is known about the humoral and, especially, cell-mediated immune response in pigs exposed to *Lawsonia intracellularis*. Pathogenesis of *L. intracellularis* has not been well investigated; however, organisms cultured in vitro have been used successfully to reproduce the disease in vivo. This bacterium has a tropism for intestinal epithelial cells, and the major pathological consequence of infection is hyperplasia of infected epithelial cells. The specific bacterial determinants, which confer pathogenicity and

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cause these distinctive pathological effects, are not known (see McCluskey et al, Infect Immun 2002 Jun; 70(6): 2899-907). Bacterial attachment and entry occur via the apical surface of immature epithelial cells in a process which appears to require a specific bacterial ligand-receptor interaction and once inside the cell, the bacteria escape from the vacuolar compartment into the cytoplasm, where they multiply and spread from cell to cell following cell division. At present, the determinants used by *L. intracellularis* to enter the cell, escape the vacuole, multiply intracytoplasmically, and modulate host cell function are not known. Therefore, the claimed outer-membrane protein induces an effective immune response such that it can be used, as a vaccine composition is not predictable in this underdeveloped art. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for any *in vivo* uses of the claimed protein. In the absence of teachings that the claimed polypeptide can generate a protective immune response, which is effective in preventing the infection or disease, the specification is not enabled for vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Applicants' arguments filed on 5/19/05 have been fully considered but they are not deemed to be persuasive.

Applicant states that a variety of guidelines are used to identify whether undue experimentation is required to identify variants, including, the teaching in the specification, the number of known variants, and the knowledge of one of skill in the art. As stated in the written description rejection, the amount of teaching in the specification is extensive, so, although there are no known variants, one of skill in the art would have sufficient teaching in the Specification to make and identify variants. In addition, the art of vaccination/immunization is one of the most sophisticated in molecular biology and, given the recent advances in the science of molecular biology, the unpredictability of this art has lessened significantly.

It is the position of the examiner that the specification discloses an isolated recombinant polypeptide comprising the amino acid sequence, SEQ.ID.NO: 1 and is immunogenic therefore, applicants are enabled for an immunogenic composition comprising the amino acid sequence SEQ.ID.NO: 1, wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant,

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or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 1. However, the specification does not disclose variants/homologues/derivatives as claimed and these variants are broader than SEQ.ID.NO: 1. Recitation of open language "comprising" in the claims does not limit to the variants of SEQ.ID.NO: 1 but reads on variants of SEQ.ID.NO: 1 plus other unknown and unlimited amino acids without any structure, property and function and are not supported by the present Specification. The limitation "at least" in the claims does not limit to any contiguous amino acids because it has no upper limit and thus reads on fragments having no limit of amino acids in length. Similarly the limitation "comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. Therefore, the claimed variants/homologues and derivatives are extremely broad polypeptides. In addition, Molloy et al (Molecular Immunol. 35, 1998, pages 73-81) teach, production of TCR (TCR comprising two other immunoglobulin super family member proteins) epitope has remained problematic as the majority of the recombinant proteins remains insoluble and is not processed. Therefore, the claimed variants of f SEQ.ID.NO: 1 for mapping T-cell epitopes must be considered highly unpredictable requiring a specific demonstration of efficacy of the polypeptide in mapping epitopes. Absent such demonstration, the invention would require undue experimentation to practice as claimed.

Further, applicant's specification does not disclose and there is no evidence of record that the claimed polypeptide/variants would generate an immune response such that one could use it for the treatment of infection or prevention. Further, as indicated above the claimed uncharacterized antigens have not been shown to induce an immune response that could prevent the infection as the claimed invention is drawn to a vaccine

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composition. The reference supplied by the examiner clearly sets forth that a single antigen may prove insignificant and a mixture of antigens capable of eliciting antibodies with more than one functional capacity may be needed. Further, the art states that in addition to candidate vaccine identification, other vaccine issues need to be answered for example, optimal mode of vaccine delivery such as parenterally delivered vaccine. Based on the general (issues) problems regarding the identification of candidate vaccine, the experimentation required to use the claimed uncharacterized antigens is "undue".

Claim Rejections - 35 USC § 102 maintained

8. The rejection for newly amended claims 1-4, 6-8, 10, 11, 13-14, 17-18 and newly added claims 40-45 under 35 U.S.C. 102(b) as being anticipated by McOrist et al, Infect Immun. 1989 March; 57 (3): 957-962 as evidenced by McOrist et al 1995 is maintained as set forth in the previous office action

McOrist et al disclose isolated polypeptide profiles obtained with Campylobacter species such as *C. mucosalis*, *C. hyointestinalis*, *C. jejuni*, *C. coli* and Campylobacter-like organism (Lawsonia intracellularis in later publications by McOrist 1995). The prior art further identifies that the protein profile obtained from Campylobacter-like organism (see figure 1) was distinct and different from other species of Campylobacter such as *C. mucosalis*, *C. hyointestinalis*, *C. jejuni*, *C. coli*. This indicates that the intracellular Campylobacter-like organism (later known as *L. intracellularis*) associated with proliferative enteropathy may be a novel bacterium with significant antigenic differences from the other Campylobacter species previously associated with the disease. The protein profiles of Campylobacter like organisms in proliferate enteritis tissue showed a 55 kD antigen (see page 959, right column). Therefore, it is likely that the 55kD major antigen identified by polyacrylamide gel electrophoresis procedure is the same as claimed polypeptide. The absence of 55 kD polypeptide in other *C. mucosalis*, *C. hyointestinalis*, *C. jejuni*, *C. coli* suggests that these organisms are antigenically different from known *C. mucosalis*, *C. hyointestinalis*, *C. jejuni*, *C. coli* and (see figure 1) and later studies recognized this Campylobacter-like organism as *L. intracellularis*. The 55 kD protein was also recognized by antisera to Campylobacter-like organism from mucosa of 1269/76 strain and in some preparations of 284/86 (Campylobacter-like organism) (see page 959 right column under immunoblotting and SDS-PAGE) and appears to be same as claimed polypeptide (i.e., *Lawsonia* spp variant) that confers a protective immune response against *Lawsonia* spp in avian and porcine as structurally similar 55 kD protein was recognized by antisera to Campylobacter-like organism from

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mucosa of 1269/76 strain and in some preparations of 284/86 . Therefore, 55 kD protein is same as FlgE polypeptide because characteristics such as amino acid sequence SEQ.ID.NO: 1 are inherent in the preparation of isolated polypeptide 55kD protein and thus read on the claimed invention including functional characteristics such as conferring protective immune response, elicits the production of antibody etc. The isolated (i.e., SDS-PAGE) 55kD antigen meet the limitations of the claims 1-4, 6-8, 10, 11, 13-14 and 17-18 (figure 1) because the claimed polypeptide is structurally (functionally) inherent in the preparation of disclosed 55kD antigen from *Lawsonia* species and thus meet the limitations of FlgE polypeptide or a variant (the broadly claimed polypeptide having 502 amino acids is almost equivalent to 55 kD of the prior art polypeptide since each amino acid molecular weight is 110 daltons). The 55kD polypeptide reads on immunogenic polypeptide as the polypeptide binds (see page 959, right column, first paragraph) to antisera raised against sonicated *Campylobacter*-like organism (*Lawsonia* spp). In the absence of evidence to the contrary that the disclosed polypeptide induces protective immune response and mimics or cross-reacts with a B-cell or T-cell epitope of *Lawsonia* spp FlgE polypeptide as this 55 kD protein reacted with rabbit antisera prepared against the intracellular (i.e., immunogenic, induces immune response) *Campylobacter*-like organisms and antisera to other *Campylobacter* species isolates did not react with preparations of intracellular organisms.

When producing an isolated 55kD polypeptide as discussed above, the composition would inherently have a carrier present, i.e., buffer for pharmaceutical use as required by claim 17. Therefore, the composition comprising an isolated 55 kD polypeptide in buffer read on vaccine composition of claims 17-18 and 40-45.

In the absence of evidence to the contrary the disclosed prior art immunogenic polypeptide and composition comprising said polypeptide and the claimed isolated or recombinant immunogenic polypeptide and composition comprising said polypeptide are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed polypeptide and composition with the 55kD protein and composition comprising said protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed polypeptide and composition and the polypeptide and composition of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594. It is acknowledged that weight is given to every term in claims. This is why the instant claims drawn to vaccine composition are scrutinized differently from a composition claim under 112, first paragraph. However, under prior art rejections, the term vaccine compositions must be weighed with the structural limitations of the claim. If the vaccine composition merely comprises a known composition, the term carries little weight absent evidence of structural difference. Of course, the existence of an unobvious structural difference would define over the prior art. Here, the prior art teaches the same polypeptide and composition as claimed. *In re Thorpe*, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). *In re Marosi*, 218 U.S.P.Q. 289, 293-293 (C.A.F.C. 1983). *In re Best*, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). *In re Brown*, 173 U.S.P.Q. 685, 688 (C.C.P.A. 1972).

Applicants' arguments filed on 5/16/05 have been fully considered but they are not deemed to be persuasive.

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Applicant states that the reference does not teach each and every element of the claimed invention and cites case laws of record. Applicant states that McOrist et al provides a protein profile of *Campylobacter* species, which contains a number of different bands from different preparations of various *Campylobacter* species, and there is no specific reference to a 55 kD protein (false positive). Further, with reference to the immunoblot using antiserum from rabbits infected with formalin-fixed whole cell antigen did not recognize 55 kD and the Examiner must provide rationale or evidence to show inherency.

With regard to Applicant's assertions that McOrist et al does not disclose the claimed invention, please note:

- (1) Page 959, bottom left column under Results through upper right column disclose, "The protein profiles of the *Campylobacter*-like organisms extracted from porcine proliferative enteropathy tissue were dominated by major protein 55 kD. Please note ^{that} the *L.intracellularis* has been extracted from infected pigs proliferative enteropathy tissue. Therefore, this is a clear evidence that the protein is the same as claimed.
- (2) Figure 2, lane 2 shows the rabbit sera (1269/76 pig infected with *L.intracellularis*) recognized the 55kD protein from mucosal preparations of 284/86 (from pigs infected with *L.intracellularis*). The absence of 55 kD polypeptide in other *C. mucosalis*, *C. hyointestinalis*, *C. jejuni*, *C. coli* suggests that these organisms are antigenically different from (see figure 1) *L.intracellularis* (i.e., no false positive). Thus the presence of 55kD protein is specific for *L.intracellularis*. Therefore the claimed polypeptide and composition and the polypeptide and composition of the prior art are same. Thus the examiner established the rejection based on scientific evidence of record.

9. The rejection of claims 1-4, 6-8, 10, 11, 13-14, 17- 18 and newly added claims 40-45 under 35 U.S.C. 102(b) as being anticipated by Panaccio M, et al, Database:

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A_Geneseq and Accession number AAW16680, WO9720050-A1 is maintained as set forth in the previous office action

Panaccio et al 1997 disclose an isolated or recombinant polypeptide (SEQ.ID.NO: 7 page 51-52 and claim 26) comprising *Lawsonia intracellularis* FlgE polypeptide variant or a peptide comprising an amino acid sequence which has comprising 60% sequence identity to SEQ.ID.NO: 1 or a homologue or derivative which mimics or cross reacts with a B-cell or T- cell epitope of *Lawsonia* spp FlgE polypeptide Database; A_Geneseq, Accession number: AAW16680/ WO9720050-A1. The disclosed peptide reads on claimed peptide because a peptide can be even two amino acids. Therefore, the disclosed peptide comprises an amino acid sequence that has 100% sequence similarity to a portion of SEQ.ID.NO: 1(see the sequence alignment) from position 64-84.

Applicant states that the claims have been amended to remove the reference to truncated variants to be pursued in separate applications. Panaccio, et al specifically teach a truncated variant which could potentially be used for protection of animals to *L. intracellularis*. Panaccio et al does not teach or suggest the variants of SEQ ID NO: 1 or a variant with 60% sequence identity to the sequence of SEQ ID NO: 1, because Panaccio et al do not teach the rest of the polypeptide.

The examiner disagrees with the applicant because the prior art discloses an isolated polypeptide comprising *Lawsonia* spp polypeptide FlgE, SEQ.ID.NO: 7 (having 120 amino acids, see SEQ.ID.NO: 7 of the art) and thus read on the present claims. Applicant's statement variants of SEQ ID NO: 1 or a variant with 60% sequence identity to the sequence of SEQ ID NO: 1, because Panaccio et al does not teach the rest of the polypeptide is not correct because the art discloses as stated above isolated polypeptide comprising SEQ.ID.NO: 7 which is a variant or homologue of FlgE.

Remarks

10. No claims are allowed.

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The Examiner regrets the inconvenience caused by referring the polypeptide as FigE instead of FlgE in the previous office action. However, the polypeptide now referred to as FlgE.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see <http://pair-direct.uspto.gov>. Should you


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have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

 Padma Baskar Ph.D.


NITA MINNIFIELD
PRIMARY EXAMINER
8/3/05